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EXAMINER	
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CATHRYN CAMPBELL
PRETTY, SCHROEDER, BRUEGGEMANN & CLARK
444 SOUTH FLOWER ST., STE. 2000
LOS ANGELES, CA 90071

DATE MAILED: 12/03/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/27/92 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-46 are pending in the application.
   Of the above, claims 2-5, 7-10 and 20-46 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 6 and 11-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-46 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

17. The specification fails to teach substantially pure subunits of UTAA. While a 100 fold purification is described, it is unclear that this constitutes substantially pure material. Applicants have described purified material which is identified only by its reactivity to anti-sera (i.e. western blots) which would fail to show contaminants. This is underscored by applicants' admission on page 36 that silver staining revealed several bands and immunostaining produced only one.

18. Applicants have argued that page 15 of the specification clearly defines what is meant by "substantially pure". Specifically, Applicants recite that it is one that after reduction (B-Me) and SDS-PAGE has a molecular weight of 90-100kD, after purification is heat stable with a mass of 590-620kD under non-reducing conditions, and has an IEP of 6.1.

19. Applicants have argued that the bands detected by silver stain are artifacts, not contaminants, and have discussed the error inherent in comparing western blot to silver stain.

20. The Examiner does not see how the Applicants' recitation of the physical properties of the molecule support a conclusion that the purified subunit is enabled. The recited properties are merely inherent to the composition. This is not the same as teaching a purified subunit. The western blot method employed teaches only that the subunit has been purified away from any immunologically cross-reactive constituents which may or may not have been present. It should be noted that the characterization "immunologically cross-reactive" can only be defined in terms of some specific antibody specificity, and therefore if such language were incorporated into the claims absent adequate definition, such claims would be indefinite. Since Applicants have argued that the silver stain method produces artifacts which may appear as proteins, it is not seen how the data derived from such a silver stain can be useful to demonstrate purity levels.

21. In contrast to Applicants assertions however, the Examiner is well aware that silver stain techniques are commonly used to demonstrate purity levels. Other conventional methods include reverse-phase HPLC for example. Since Applicants have called into question their method for determining purity, and have failed to provide other commonly accepted indices of purity, the specification cannot be said to teach substantially purified subunit.

22. The specification fails to teach the administration of any vaccine which inhibits cancer in the recipient.

23. While the specification does teach the administration of a composition which increases antibody titer to U-TAA, there are no teachings that this titer increase is indicative of cancer inhibition in vivo.

24. Applicants have relied upon page 17, lines 5-13 of the specification for teaching of inhibition of cancer. The teaching appears to be speculative and is not considered sufficient to meet the enablement requirement.

25. The specification fails to teach a vaccine containing the composition of claim 1. Nowhere does the specification teach immunization with substantially purified material, as argued above.

26. The Examiner maintains that Applicants have failed to teach substantially pure subunits. The Examiner concedes that Applicants have taught a 100-fold purification of U-TAA a page 23 of the specification, and consequently have probably taught a 100-fold purification of U-TAAs constituent subunits, but a 100-fold purification is not predictive of "substantially pure" material. Applicants physical description of the subunit does not adequately define the scope of the term "substantially pure".

27. Additionally, since Applicants are claiming the subunit and a vaccine containing substantially pure forms thereof, inclusion of the entire U-TAA complex in the composition (as obtained by Example 1 and used for immunization in example 3) by definition would comprise a subunit that was **not** substantially pure. In fact, the only place in the specification where the subunit appears alone is on the western blot, the problems with which in determining purity levels are discussed above.

28. The Deposit requirement made in the prior office action will be maintained because Applicants have explicitly claimed a vaccine which requires the use of these cells (claim 12). While the Examiner does not dispute that cells similar to those claimed could perhaps be developed by the skilled artisan, it would be

impossible for the skilled artisan to develop cells identical in every way to those instantly claimed, a requirement to practice the invention as claimed in claim 12.

29. Claims 1, 6 and 11-19 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

30. Claims 1 and 6 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

31. It is unclear what is meant by "substantially purified" in claim 1. It is unclear what is meant by "reagents" in claim 6. It is also unclear what is meant by "reactive" in claim 6.

32. Applicants have argued that the term "substantially purified" is adequately defined in the specification. Applicants have pointed to page 17, lines 15-22 for the definition of "reagents" and "reactive" as used in claim 6.

33. As argued above, the Examiner does not agree that the term "substantially purified" has been adequately defined in the specification. With respect to claim 6, the cited portion of the specification does recite that such reactive reagents can be anti-idiotype antibodies. The specification is silent as to what else such reagents can be. It should be noted that the restriction requirement originally made in this case specifically classified claims 6 and 7 in their own Group, Group VI, but included claim 6 in Group I as well. It appears that this classification ambiguity was the result of the ambiguous language of claim 6. If Applicants were to amend claim 6 to specifically recite anti-idiotype antibodies, the claim would be drawn to a non-elected invention. If Applicants consider claim 6 as only drawn to anti-idiotype antibodies, then claim 6 should be withdrawn from consideration as being drawn to a non-elected group. If Applicants consider claim 6 to be drawn to compositions other than anti-idiotypes, then the specification fails to teach such reagents. It should be noted however that in examining the claims for novelty, the Examiner is interpreting claim 6 in its broadest sense, that is to say that the antigen with which the antibody reacts is a reagent specific for the antibody. Also, enzyme labelled anti-antibody, as would be used in immunoassay methods also anticipate this claim under the current interpretation of its meaning.

34. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

35. Before specifically discussing the prior art rejections, the Examiner feels that it would be useful to restate his interpretation of the teachings provided by the specification, and his interpretation of the claims being examined.

36. As discussed above, the Examiner does not agree that a substantially purified subunit has been taught by the specification. At best, the skilled artisan would have to perform the outlined purification scheme, and then determine the purity level achieved. This purity level would then function to define "substantially pure" as used in the instant application. Unfortunately, the Examiner does not have facilities required to make this empirical determination. He must therefore rely upon the disclosure to ascertain the scope of the claimed language. As discussed above, Applicants have pointed to the physical description of the subunit as defining the term "substantially pure". The Examiner has outlined the inadequacy of such a definition above. Absent a sufficient definition for this term, the Examiner must apply references which appear to teach the same protein or complex, and which based upon a reasonable reading appear to provide a commensurate level of purity as disclosed instantly. For example, if a cited reference teaches that the urine is concentrated and then applied to a gel filtration column, as Applicants have done in example 1, then that reference would anticipate claim 1 for example, even though it is equally unclear what absolute purity level was achieved by the prior art.

37. Claims 1 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by N.S. Rote et al, 1980.

38. Rote et al describe purification schemes of tumor associated antigens found in the urine. They teach the use of centrifugation and concentration (p. 204) followed by gel-filtration (p. 205).

39. Applicants have argued that Rote et al do not define any antigen allegedly purified, nor was a molecular species identified. Further, Rote et al failed to make antibodies reactive to any antigen. The Experiments of Rote et al are characterized by Applicants as being prone to false positive results. Rote et al use the less effective Sepharose-6B to purify samples.

40. It is the Examiner's position that the purification method employed by Rote et al would have resulted in the purification of Applicants instantly claimed subunit to a degree commensurate with that instantly claimed. It is not necessary that Rote describe the physical characteristics of his antigens for his antigens to anticipate that instantly claimed. Such physical characteristics are inherent to the compound, and therefore need not be described in the prior art for anticipation. If Applicants believe that the experiments and resin used by Rote et al would not yield the same purity as instantly achieved and claimed, then evidence to that effect is solicited by the Examiner.

41. Claims 1 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Francisco X. Real et al, U.S. Patent 4,562,160.

42. Real et al teach the purification of a 90kD glycoprotein tumor antigen. It is unclear if this is the same antigen being claimed in claim 1 of the instant application.

43. Applicants arguments are somewhat confusing. Applicants have mainly argued by describing their invention, as opposed to identifying the differences between the protein of the prior art and the protein of the invention. Applicants have however argued that the IEP's are different for the 2 proteins, but only by 1/2 of a pH unit.

44. As Applicants themselves have pointed out in the specification, the U-TAA is not restricted to urine, but is expressed on tumor cells as well. The difference in isoelectric points reported is well within experimental error, and it is the Examiner position that the burden has been shifted to Applicants show that the protein of Real et al does not anticipate the instantly claimed protein.

45. Claims 1, 6, 18 and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Joseph P. Brown et al, U.K. patent GB 2188637A.

46. Brown et al teach the sequence and purification of a melanoma antigen p97. They teach the fabrication of a vaccinia vaccine containing p97 and the immunization of animals with this vaccine to produce antibodies. It is unclear if the p97 of Brown et al is the same as the 90-100kD protein of the instant application. This seem likely in view of the disclosure of Gupta et al, 1984 abstract of the similarity between UTAA and antigens produced by melanoma cells.

47. Applicants have argued that the protein of Brown has been sequenced, and is a sialoglycoprotein which is structurally related to serum transferrin.

48. It is not seen how this argument shows that the protein of Brown does not anticipate the cited claims. Have Applicants shown that the claimed subunit is not a sialoglycoprotein? Have they shown what the structure of the subunit is?

49. Claims 11 and 14-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by R.K. Gupta et al, 1987 abstract.

50. Gupta et al teach the vaccination of melanoma patients with tumor cells, at least one of which (M14 cells) expresses melanoma tumor associated antigen. It seems likely that the cell line also produces UTAA in light of the disclosure of Gupta et al, 1984 abstract. Applicants disclosure supports this assertion (p53-54).

51. Applicants have discussed the requirements of 35 USC 102. Applicants have characterized their invention as a polypeptide subunit of UTAA.

52. The invention of claims 11 and 14-17 is not a polypeptide subunit, but rather a vaccine and a method of its use. The vaccine comprises tumor cells having UTAA on their surface. Gupta 1987 teach such a vaccine, and its use.

53. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

54. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

55. Claims 1 and 6 are rejected under 35 U.S.C. § 103 as being unpatentable over D.M. Euhus et al, 1988 abstract.

56. It would have been obvious to affinity purify the UTAA using the monoclonal antibody AD1-40F4 disclosed by Euhus et al, 1988 abstract. The motivation for doing so would be the use of the purified material to produce polyclonal antisera to the protein for use in diagnostic procedures.

57. Applicants have argued that there is no suggestion in the Euhus reference to purify the antigen. Applicants point out that IgM antibody is difficult to affinity purify, and that the technology did not exist at the time Euhus was published to permit successful purification of IgM antibody.

58. These arguments are not persuasive. Applicants have provided no evidence that IgM antibodies could not have been purified in 1988, and it is doubtful that such evidence could be produced, based upon the Examiners own experience. Additionally, it is not requisite that the ability to purify the antigen existed on the date the publication issued, merely that it antedates the instant invention. These issues are merely ancillary however. Euhus were able to use their monoclonal in an immunoassay, and therefore sufficient purity levels were achieved for such an analytical technique. Such purity levels would have been more than adequate to purify ligand. They also describe the serum component (i.e. the antigen) as "purified". Additionally, they disclose the use of polyclonal antibodies in an assay, and therefore the motivation for production of polyclonal antibodies, and hence pure antigen, is contained in this reference.

59. Claim 12 is rejected under 35 U.S.C. § 103 as being unpatentable over J.H. Wong et al, 1988 and R.K. Gupta et al, 1987 abstract.

60. As outlined above, Gupta et al, 1987 abstract disclose the use of melanoma cell lines in vaccine preparations, including M14.

61. Wong et al, 1988 disclose that M10, M14 and M24 are melanoma cell lines and that M10 and M14 are known to express melanoma tumor associated antigen.

62. It would have been obvious to use any known melanoma cell line, including M10, which expresses the appropriate antigens. To do so would confer the appropriate antibody response.

63. Applicants have erroneously argued the references separately. Applicants also argue that Wong teaches that M24 does not express M-TAA.

64. Wong does fail to detect M-TAA on M24 cells, but does find antigens reactive with patient sera on all 3 cell lines which was not anti-HLA.

65. Claim 13 is rejected under 35 U.S.C. § 103 as being unpatentable over Wong et al, 1988 and Gupta et al, 1988 abstract as applied to claim 12 above, and further in view of Jean-Claude Bystryn et al, 1986.

66. Bystryn et al disclose that transplantation antigens are undesirable contaminants in melanoma vaccines derived from tumor cells.

67. It would have been obvious to use tumor cells which expressed HLA antigens identical to those found in the recipient in order to avoid an immune response from the recipient to such antigens.

68. Applicants have erroneously argued the references separately, and further have argued that at the time of publication of Bystryn et al HLA matching was not sufficiently advanced to a point where it was a feasible alternative. Applicants have provided no evidence in support of this statement.

69. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

70. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 308-4227

71. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Chris Dubrule whose telephone number is (703) 308-4240. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CJD

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180